REMARKS

This Amendment cancels claims 11-22 and amends claim 23. The replacement of "mucosal" with --oromucosal-- in claim 23 is supported by page 3, lines 3-4. Claims 23-32 are pending.

A Request for Continued Examination is attached. Entry and consideration of this Amendment are accordingly requested.

Examiner Gembeh is thanked for allowing claims 18, 21, 22 and 30. This Amendment places the entire application in condition for allowance for the reasons discussed below.

This Amendment overcomes the 35 U.S.C. § 112, first paragraph, rejection of claims 11, 14-17, 19, 20, 23 and 26-32 for failure to adequately describe the "derivative" of formula I. Claims 11-22 have been canceled. Claim 23 has been amended by deleting "derivative" in accordance with the Examiner's helpful suggestion. Reconsideration and withdrawal of the written description rejection of claims 11, 14-17, 19, 20, 23 and 26-32 are earnestly requested.

The 35 U.S.C. § 112, first paragraph, rejection of claims 11, 14-17, 19, 20, 23 and 26-32 for failure to adequately describe "preserving agents" is respectfully traversed.

The traditional test for compliance with the written description requirement is whether the application clearly allows

persons of ordinary skill in the art to recognize that the inventor invented what is claimed, In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention as now claimed, Vas-Cath, supra. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed, In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). See also "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, para. 1. "Written Description" Requirement," MPEP § 2163, especially at "I.A. Original Claims", page 2100-174.

"Preserving agents" is part of the original claimed invention. Original claim 3 expressly recited "preserving agents", and original claim 5 specified a Markush grouping from which the preserving agent is selected. Original claim 7 defined a formulation which included a mixture of two preserving agents, and original claim 10 set forth a process for preparing a formulation whose first step included mixing and dissolving two preserving agents in combination with ethanol, purified water ans aspartame. In short, the application is entitled to a strong presumption that

it includes an adequate written description of the invention, Wertheim, id.

Another factor to consider is the knowledge and level of skill in the art. Knowledge and skill in the preservation art are high, as demonstrated by Takuri et al., "Preservation of Dispersed Systems," 2 Pharmaceutical Dosage Forms 73-114 (Lieberman, Rieger and Banker eds. 1989), who discuss the ideal preservative, microbial contamination, various classes of preservatives, and how to evaluate preservation efficacy.

The application as filed identifies preferred preserving agents as lower alkyl parahydroxybenzoates, especially methyl and propyl parahydroxybenzoate (Specification, page 2, line 32-33). Takuri et al. discuss the use of these esters at pages 90-91. Accordingly, one of ordinary skill in the oromucosal dosing arts, having read the application's disclosure of preserving agents, would immediately envisage what preservatives would be suitable for use in the claimed oromucosal formulation. He would also know, as evidenced by Takuri et al., how to determine which preserving agents would be appropriate for the oromucosal formulation of the present invention without performing undue experimentation. In short, he would recognize the applicants were in possession of the

preserving agents of the presently-claimed invention as of the filing date of the application. Reconsideration and withdrawal of the written description rejection of claims 11, 14-17, 19, 20, 23 and 26-32 are earnestly requested.

The 35 U.S.C. § 102(b) rejection of claims 23-25 over U.S. Patent No. 5,498,623 to Karjalainen et al. is traversed. The claimed method requires oromucosal administration to a patient, i.e., administration via the *oral* mucosa, not through the stomach intestines. An oromucosal formulation must disintegrate and dissolve locally so that absorption of the formulation will occur in the patient's mucous membranes of the oral cavity, such as the alveolar mucosa, gingival mucosa and pharyngeal mucosa.

Karjalainen et al. fails to disclose oromucosal administration of its composition. Instead, Karjalainen et al. discloses its compounds may be administered orally, parenterally or intravenously (Col. 4, lines 60-64).

Oral administration is not oromucosal administration. Instead, formulations which are orally administered are designed to be swallowed and distintegrate/dissolve in the gastric tract to permit absorption, typically in the duodenum. Reconsideration and

withdrawal of the anticipation rejection of claims 23-25 are earnestly requested.

The 35 U.S.C. § 103(a) rejection of claims 11-17, 19, 20, 23-29, 31 and 32 over Karjalainen et al. in view of U.S. Patent No. 5,658,938 to Geerts et al., U.S. Patent No. 6,326,401 to Chauveau et al. and Huupponen et al., 58 Clin.Pharmacol.Ther. 506-11 (1995) is respectfully traversed. A feature of the claimed method of administration is that the formulation is administered to a patient by oromucosal administration.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method because one of ordinary skill in the art would not combine their disclosures as suggested by the Patent Office, or have a reasonable expectation that the combination would be successful. Neither Karjalainen et al. nor Geerts et al. disclose or suggest oromucosal administration of a substituted imidazole conforming to formula (I). Instead, Karjalainen et al. expressly teaches oral administration of its substituted imidazole. In short, one of ordinary skill in the art has no apparent reason or motivation from Karjalainen et al. or Geerts et al. to administer the substituted imidazole of formula (I) oromucosally.

The remaining references also fail to provide the motivation absent from Karjalainen et al. and Geerts et al. Thus, Chauveau et al. provides a narrow disclosure of oromucosal formulations which contain an active ingredient in combination with less than 5 % of capryl caproyl macrogel glycerides. The entire thrust of Chauveau et al. is directed to the utility of capryl caproyl macrogel glycerides in such formulations. See Col. 5, lines 16-59. One of ordinary skill in the art is thus given no apparent reason to modify Karjarlainen et al. to arrive at the claimed invention.

Huupponen et al. differs from the claimed invention because atipamezole does not contain a halogen or hydroxyl at R_1. Neither halogen or hydroxyl are bioisoteric with the hydrogen in atipamezole. Accordingly, one of ordinary skill in the art would not be motivated to substitute Karjalainen et al.'s substituted imidazole for Hupponen et al.'s atipamezole. Moreover, one of ordinary skill in the art would not have a reasonable expectation that such a substitution would be successful, due to the known problem of cardiac safety associated with fipamezole.

Oral administration of a substituted imidazole derivative conforming to formula (I) has been associated with compromised cardiac safety at systemic concentrations of about 2000 ng/ml

(Specification, page 1, line 31 to page 2, line 2 and Example 8). Oral administration requires the drug to pass through the liver - and be subject to metabolic action - before reaching the heart. A person of ordinary skill would assume oromucosal administration of fipamezole would compromise cardiac safety to a greater extent than oral administration because the drug would be absorbed through the oral mucosa into the bloodstream and then carried directly to the patient's heart without any metabolic action by the liver. Accordingly, one of ordinary skill would not have a reasonable expectation that oromucosal administration of fipamezole would be successful.

Finally, even assuming, arguendo, the cited references would lead one of ordinary skill to the claimed invention, the unexpected results achieved by oromucosal administration rebut any prima facie case of obviousness. As noted above, oral administration of a substituted imidazole derivative conforming to formula (I) has been associated with compromised cardiac safety at systemic concentrations of about 2000 ng/ml. The applicants unexpectedly discovered fipamezole's problems of compromised cardiac safety and rapid decomposition can be avoided by oromucosal administration

even at systemic concentration levels of up to 3,300 ng/ml. See Example 8.

Nothing in the cited references suggests oromucosal administration of fipamezole will avoid the problem of compromised cardiac safety. Accordingly, the results shown in Example 8 would be considered unexpected by one of ordinary skill in the art.

Reconsideration and withdrawal of the obviousness rejection of claims 11-17, 19, 20, 23-29, 31 and 32 are earnestly requested.

This Amendment overcomes the provisional obvious-type double patenting rejection of claims 11-17 and 19 over claims 1-3 and 12-18 of U.S. application S.N. 10/534,117. Claims 11-22 have been canceled. Pending method of administration claims 23-32 are patentably distinct from solid dosage composition claims 1-3 and 12-18 of the '117 application. Reconsideration and withdrawal of the obvious-type double patenting rejection are earnestly requested.

A Supplemental Information Disclosure Statement is attached.

It is believed the application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 11-17, 19, 20, 23-29, 31 and 32, and issuance of a Notice of Allowance directed to claims 23-32, are respectfully requested. The Examiner

is urged to telephone the undersigned should she believe any further action is required for allowance.

The RCE filing fee is being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to charge our Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

James C. Lydon
Reg. No. 30,082

Atty. Case No.: **TUR-168**
100 Daingerfield Road
Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

Enclosures:
Request for Continued Examination
Supplemental Information Disclosure Statement